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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,052	04/09/2007	Paul A. Bunn Jr.	5941-65-PUS	7009

22442 7590 12/12/2008

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
12/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,052	BUNN JR. ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,49,51-53,55-59 and 66-81* is/are pending in the application.

4a) Of the above claim(s) *51,52,59,68-72 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,49,55-58,66,67,73,74 and 76-81* is/are rejected.

7)☒ Claim(s) *76-81* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 9/12/08 in response to the Office Action of 3/11/08 are acknowledged and have been entered.

Claims 76-81 have been added by Applicant.

Claims 48, 49, 51-53, 55-59, and 66-81 are pending.

Claims 51, 52, 59, 68-72, and 75 have been withdrawn.

Claims 48, 49, 51, 52, 55-59, and 66-75 have been amended by Applicant.

Claims 48, 49, 55-58, 66, 67, 73, 74, and 76-81 are currently under examination.

This Office Action contains new objections necessitated by amendments.

Rejections Withdrawn

The rejection under 35 U.S.C. 112, second paragraph, is withdrawn.

New Objection

Claims 76-81 are objected to for apparent typographical errors. Claims 76-81 recite: "…predicted to benefit from therapeutic administration of the EGFR inhibitor, and agonist thereof, or a drug having substantially similar biological activity as the EGFR inhibitor…". The word "and" appears out of place. It is suspected Applicant intended claims 76-81 to recite: "…predicted to benefit from therapeutic administration of the EGFR inhibitor, ~~and~~ **an** agonist thereof, or a drug having substantially similar biological activity as the EGFR inhibitor…". Proper correction is required.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48, 49, 55-58, 66, 67, 73, and 74 remain rejected and claims 76-81 are rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement for the reasons stated in the Office Action of 3/11/08 and for the reasons set-forth below.

The specification, while being enabling for a method to select a cancer patient who is predicted to benefit from therapeutic administration of gefitinib comprising detecting the level of E-cadherin polynucleotides in a sample of tumor cells from said patient, comparing said level to a level of E-cadherin polynucleotides in a sample of tumor cells from a subject having the same type of cancer and that is resistant to gefitinib, and selecting the patient as being predicted to benefit from therapeutic administration of gefitinib if the level of E-cadherin polynucleotides in the sample of tumor cells from said patient is higher than the level of E-cadherin polynucleotides in the sample of tumor cells from the subject that is resistant to gefitinib, **the specification does not reasonably provide enablement for** methods to select a cancer patient who is predicted to benefit from therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor, comprising detecting polynucleotide expression levels of E-

cadherin in a sample of tumor cells from a patient, comparing the levels to just any level of expression of E-cadherin that anyone has correlated with sensitivity or resistance to just any EGFR inhibitor, and selecting the patient as being predicted to benefit from a therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor if the polynucleotide or polypeptide expression level of E-cadherin in the patient's tumor cells is statistically more similar to just any expression level of E-cadherin that anyone has correlated with sensitivity to just any EGFR inhibitor than to resistance of just any EGFR inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods to select a cancer patient who is predicted to benefit from therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor, comprising detecting polynucleotide expression levels of E-

cadherin in a sample of tumor cells from a patient, comparing the levels to just any level of expression of E-cadherin that anyone has correlated with sensitivity or resistance to just any EGFR inhibitor, and selecting the patient as being predicted to benefit from a therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor if the polynucleotide or polypeptide expression level of E-cadherin in the patient's tumor cells is statistically more similar to just any expression level of E-cadherin that anyone has correlated with sensitivity to just any EGFR inhibitor than to resistance of just any EGFR inhibitor. It is noted that drugs having substantially similar biological activity as an EGFR inhibitor broadly encompass every drug that treats cancer, as treating cancer is a biological activity of EGFR inhibitors.

The specification teaches a method to select a non-small cell lung cancer patient who is predicted to benefit from therapeutic administration of gefitinib comprising detecting the level of E-cadherin polynucleotides in a sample of tumor cells from said patient, comparing said level to a level of E-cadherin polynucleotides in a sample of tumor cells from a subject that is resistant to gefitinib, and selecting the patient as being predicted to benefit from therapeutic administration of gefitinib if the level of E-cadherin polynucleotides in the sample of tumor cells from said patient is higher than the level of E-cadherin polynucleotides in a sample of tumor cells from a subject that is resistant to gefitinib (see page 42, in particular). In regards to claims such as 57, 58, and 74, drawn to methods wherein *any* expression of E-cadherin is predictive of a benefit from EGFR inhibitor, it is noted that the specification discloses that *both* gefitinib-sensitive and

gefitinib-resistant patients express E-cadherin polynucleotides (see page 42, in particular). Therefore, the specification provides evidence that the claimed methods are not enabled in commensurate with the scope of the claims. Further, the specification does not provide a working example using any drug other than gefitinib. Further, the specification does not demonstrate comparisons using just any level of expression of E-cadherin that could possibly be correlated with sensitivity or resistance to just any EGFR inhibitor.

The level of unpredictability for using a particular molecule to identify a patient that would be responsive to a particular therapy is quite high. The state of the prior art dictates that if a molecule such as E-cadherin polynucleotide is to be predictably used as a surrogate for a particular diseased state (such as a non-small cell lung cancer patient who is predicted to benefit from therapeutic administration of gefitinib), one must demonstrate a particular expression pattern of E-cadherin polynucleotide correlates with said particular diseased state. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. While Tockman et al is drawn to using a particular biomarker to diagnose a particular disease, the teachings of Tockman et al exemplify the state of the prior art for using a particular molecule to indicate a particular diseased state. In the instant situation, the particular diseased state is a cancer that is resistant or responsive to a particular type of therapy. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish

quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. Absent evidence of a correlation between a particular expression pattern of a particular molecule and a particular diseased state, one of skill in the art would not predict that said particular expression pattern of said particular molecule is indicative of said particular diseased state without undue experimentation. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods to select a cancer patient who is predicted to benefit from therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor, comprising detecting polynucleotide expression levels of E-cadherin in a sample of tumor cells from a patient, comparing the levels to just any level of expression of E-cadherin that anyone has correlated with sensitivity or resistance to just any EGFR inhibitor, and selecting the patient as being predicted to benefit from a therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor if the polynucleotide or polypeptide expression level of E-cadherin in the patient's tumor cells

is statistically more similar to just any expression level of E-cadherin that anyone has correlated with sensitivity to just any EGFR inhibitor than to resistance of just any EGFR inhibitor, and Applicant has not enabled said methods because it has not been shown that tumor cells from a patient with a cancer having levels of E-cadherin polynucleotides that are statistically more similar to just any polynucleotide expression level of E-cadherin that anyone has correlated with sensitivity to just any EGFR inhibitor than to resistance of just any EGFR inhibitor would predictably determine that said patient would benefit from therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

In the Reply of 9/12/08, Applicant states that one of skill in the art understands that inhibition of EGFR activity represents a common mechanism of action for all of the recited EGFR inhibitors, agonists thereof, or drugs having substantially similar biological activity as EGFR inhibitors and that a showing of resistance or sensitivity to agents that interact with this common mechanism is extended to all those therapeutic agents that share this common mechanism of action. Applicant further argues that gefitinib shares the same mechanism of action as the claimed family of compounds.

The amendments to the claims and the arguments found in the Reply of 9/12/08 have been carefully considered, but are not deemed persuasive. The Examiner agrees that inhibition of EGFR activity represents a common mechanism of action for all of the recited EGFR inhibitors. However, inhibition of EGFR activity is not a required mechanism of recited agonists of EGFR inhibitors or drugs having substantially similar biological activity as EGFR inhibitors.

In regards to the argument that gefitinib shares the same mechanism of action as the claimed family of compounds, one of skill in the art would recognize that EGFR inhibitors, agonists thereof, and drugs having substantially similar biological activity as EGFR inhibitors do not share the same mechanism. For instance, Engelman et al (Cancer Research, December 2007, 67: 11924-11932) teaches that EGFR inhibitors do not share the same mechanisms of inhibiting EGFR. Specifically, Engelman et al teaches the EGFR inhibitors gefitinib and erlotinib act as ATP mimetics, while PF00299804 acts as an ATP mimetic and also binds Cys-797 of EGFR (gefitinib and erlotinib do not bind Cys-797 of EGFR) (right column of page 11924, in particular). The ability of PF00299804 to bind Cys-797 of EGFR enables PF00299804 to inhibit EGFR in the presence of EGFR T790M (see abstract, in particular); however, EGFR with a T790M mutation results in resistance to gefitinib and erlotinib (see page 11924, in particular). Therefore, the claimed family of compounds clearly does not share the same mechanism of activity in such a manner that would enable one to predictably substitute one for another in order to perform the claimed method with any predictability of success. While the specification teaches expression of polynucleotides that are

differentially expressed based on gefitinib sensitivity, one of skill in the art would not expect said polynucleotides to be differentially expressed in the same manner in patients that are predicted to benefit from just any EGFR inhibitor, agonists thereof, and drugs having substantially similar biological activity as EGFR inhibitors due to difference in functional mechanisms of EGFR inhibitor, agonists thereof, and drugs having substantially similar biological activity as EGFR inhibitors. Further, undue experimentation would be required to identify polynucleotides that are differentially expressed in patients that are predicted to benefit from a particular EGFR inhibitor, agonists thereof, and drugs having substantially similar biological activity as EGFR inhibitors. Such experimentation is prophetically proposed in the paragraph bridging pages 9 and 10 of the instant specification.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 48, 49, 55-58, 66, 67, 73, 74, and 76-81 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 11/781946. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-15 of copending Application No. 11/781946 are drawn to a species of instant claims 48, 49, 55-58, 66, 67, 73, 74, and 76-81.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In the Reply of 9/12/08, Applicant argues that this provisional rejection will be addressed once allowable subject matter has been identified.

Summary

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/

Examiner, Art Unit 1642